REMARKS

With this Response, claims 2, 3, 4, 13, 15-17, 25-27, 34-36, and 42 are canceled. Claims 1, 5, 12, 14, 18, 24, 28, 33, 37, and 43 are amended. As such, claims 1, 5-12, 14, 18-24, 28-33, 37-41 and 43 are now pending. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Objection To The Drawings:

The August 5, 2004 Office Action objected to FIGS. 1 and 2, stating:

> Figures 1 and 2 should be designated by a legend such as --Prior Art--because only that which is old is illustrated. See MPEP § 608.02(g). Corrected drawing sheets are required in reply to the Office action to avoid abandonment of the application. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance. (August 5, 2004 Office Action; Page 2).

With this Response, FIGS. 1 and 2 have been amended to include the legend "Prior Art." Please find enclosed: Replacement Sheet displaying FIG. 1, Replacement Sheet displaying FIG. 2, a sheet illustrating the changes made to originally filed FIG. 1 (changes shown in red), a sheet illustrating the changes made to originally filed FIG. 2 (changes shown in red), and Applicant has resubmitted original FIGS. 3-7 (for completeness). As such, Applicant respectfully requests that the objection to the drawings be withdrawn.

Objections To The Specification:

The August 5, 2004 Office Action objected to the specification, stating:

> The disclosure is objected to because of the following informalities: on page 9, line 15, a word, such as "flow" or "force" appears to have been omitted after "electroosmotic". (August 5, 2004 Office Action; Page 2).

With this Amendment, Applicant has amended the above-identified passage to recite "electroosmotic flow" in accordance with the Office Action's suggestion. As such, Applicant respectfully requests removal of this objection to the specification.

Additionally, the Office Action stated:

> The use of the trademark TRITON X-100 has been noted in this application. **It should be capitalized wherever it appears and be accompanied by the generic terminology (i.e. 4-(1 ,1 ,3,3-Tetramethylbutyl)phenyl-polyethylene glycol)**.
>
> Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. (August 5, 2004 Office Action; Pages 2-3)(Emphasis added).

In response, Applicant has made the suggested amendments. As such, Applicant respectfully requests removal of this objection to the specification.

Claims Rejected Under 35 U.S.C. §112:

The August 5, 2004 Office Action rejected claims 2, 15, 25, and 34 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention, stating:

> These claims are limited to a "first channel compris[ing] a slight charge", and depend from claims limited to "a first uncharged channel." It is unclear whether uncharged or slightly charged channels are intended, and to what degree channels in the claimed devices and methods can be charged. (August 5, 2004 Office Action; Page 3).

With this Response, Applicant has cancelled claims 2, 15, 25, and 34. As such, the rejection under 35 U.S.C. §112, second paragraph is obviated.

Claims Rejected Under 35 U.S.C. §102:

The August 5, 2004 Office Action rejected claims 1, 2, 6-9, 11, 12, 15, 19-22, 24, 25, 29, 30, 32-34, 38, 39, and 41 under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over U.S. Published Application No. 2002/0112959 A1 to Xue et al. More specifically, the Office Action rejected independent claims 1, 12, 24, and 33, stating:

> Further addressing **claims 1, 12, 24, and 33**, and addressing claims 2, 15, 25, and 34, **Xue et al do not explicitly address the amount of charge present on the walls of the first and second channels.**

> However, their example of Paragraph 0071 and Figure 9 shows elution of anions and cations into opposite channels, indicating substantial absence of electroosmotic flow, and therefore, either uncharged or slightly-charged channel walls, as supported by the specification of the instant application (Page 8, lines 11-18). Additionally, any surface in contact with a polar solution and subjected to an electric field will carry some degree of charge, strictly speaking. (e.g. acidic silanol groups in glass, trapped polar impurities in nonpolar polymers, or induced polarization) The disclosed apparatus of Xue et al successfully performs the same function with the same structure as in the instant claims, and thus the separation channels must possess similar charge characteristics. Any further reduction of channel charge would constitute an obvious improvement, because it would provide faster anion migration, given a net negative channel charge.

To overcome the rejections under 35 U.S.C. §102(e), Applicant has amended independent claim 1 (by incorporating claims 3 and 4 into claim 1), amended independent claim 12 (by incorporating claims 16 and 17 into claim 12), amended independent claim 24 (by incorporating claims 26 and 27 into claim 24), and amended independent claim 33 (by incorporating claims 35 and 36 into independent claim 33). **As such, each independent claim requires an uncharged first column having a coating and an uncharged second column having a coating**. Further, the Applicant has amended each independent claim to require **the first uncharged column engaged to a first microfluidic system for proteome analysis**. Since the Xue et al. reference does NOT expressly or inherently contain each limitation of the claimed invention, the Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. §102(e).

To anticipate a claim, the reference must teach every element of the claim. M.P.E.P. 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); M.P.E.P. 2131. "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989); M.P.E.P. 2131.

As disclosed in the Applicant's specification, the claimed invention utilizes an uncharged column to avoid sample loss and allow for the use of a small amount of sample. Further, the

Applicant found that coating the column increased the efficiency of the claimed invention. More specifically, the specification discloses:

> The present invention provides an apparatus and method of utilizing bi-directional capillary electrophoresis ("CE"). In one aspect of the invention, the bi-directional CE device comprises an uncharged capillary or column. In one aspect of the present invention, the uncharged capillary or column allows for minimal interaction between the sample and the walls of the capillary or column. **The minimal interaction between the sample and the uncharged capillary or column allows for minimal sample loss. In one aspect of the invention, the capillary or column is coated to minimize the charge on the capillary or column.** In one aspect of the invention, electroosmotic flow is minimized in the capillary or column. In one aspect of the invention, cations and anions are simultaneously separated from the sample. (Page 3, Line 25-Page 4, Line 6)(Emphasis added).

> **The use of no or low electroosmotic is of increasing importance as advancements are being made in the coating of capillaries and microchannels to minimize analyte adsorption to the capillary or microchannel walls. Such coatings allow for minimal interaction between samples and the walls of the device; less interaction relates to smaller sample losses. Reducing sample loss means smaller quantities of starting materials can be utilized.** The generation of electroosmotic flow requires the presence of ionizable groups on the surface of the capillary or microchannel channel walls. **However, these ionizable groups also lead to unwanted to charge based interactions that can lead to sample loss and peak broadening. Minimizing or negating charge interactions at the capillary or microchannel wall/solution (solid/liquid) interface is necessary to avoid these interactions.** (Page 9, Lines 15-24)(Emphasis added).

As indicated in the Office Action, the Xue et al. reference does NOT expressly disclose an uncharged column; further, the Xue et al. reference does NOT expressly disclose coating the column to render an uncharged column. Further, the Xue et al. reference never discloses a device capable of reducing sample loss or minimizing the needed amount of starting material. The Office Action concludes that use of an uncharged column and the subsequent benefits are inherent in the Xue et al. reference because the device appears to perform the same function; further, the Office Action concludes that coating the column to render a column uncharged and improve performance is inherent in the Xue et al. reference.

Applicant respectfully disagrees with this conclusion. The claimed invention recites a device and method of efficiently separating cations and anions from a sample; further, the

claimed device and method, as amended, efficiently utilize columns which have been coated to render the column uncharged in order to ensure minimal sample loss and therefore allow for the use of reduced amounts of starting materials. Because these problems are never discussed in the Xue et al. reference, Applicant respectfully disagrees that solutions to these problems could be inherently found in the Xue et al. reference.

In addition, the Applicant has amended each independent claim to require that the first uncharged, coated column engages a first "**microfluidic system for proteome analysis**". The Xue et al. reference does NOT disclose such a downstream approach or method. As such, Applicant respectfully requests the removal of Xue et al. as a 35 U.S.C. §102(e).

Regarding the microfluidic system for proteome analysis, the Applicant's specification discloses:

> **FIG. 5 shows an embodiment of the present invention in which the bi-directional capillary electrophoresis separation device 9 has been incorporated into an integrated microfluidic system for proteome analysis 31.** Assignee's co-pending U.S. Patent Application Ser. No. 10/273,494, the entirety of which is hereby incorporated herein by reference, discloses an integrated microfluidic system for proteome analysis.
>
> **In one aspect of the present invention, the integrated microfluidic proteome analysis system 31 comprises an upstream separation module, preferably a multi-dimensional chromatography device comprising one or more separation columns or channels interfaced with at least one microfluidic module.** The microfluidic module comprises a microfluidic device which is a substrate comprising one or more recipient channels for receiving substantially purified polypeptides from the upstream separation module. Preferably, the microfluidic device is covered by an overlying substrate which comprises openings communicating with the one or more channels of the device and through which solutions and/or reagents can be introduced into the channels. The overlying substrate also maintains the microfluidic module as a substantially contained environment, minimizing evaporation of solutions flowing through the channels of the microfluidic device.
>
> In a preferred aspect, **proteases are immobilized in one or more channels of a protease digestion device of at least one microfluidic module of the integrated microfluidic system for proteome analysis 31 generating an "on-device" protein digestion system. Still more preferably, as polypeptides travel through channels of the**

microfluidic module by mass transport, they are concentrated as they are digested by the proteases. In one aspect of the present invention, the microfluidic module is coupled at its downstream end to **a downstream separation module (e.g., such as a capillary electrophoresis or CE module)** which collects digested polypeptide products, i.e., peptides, and which can perform further separation of these peptides. The downstream separation module is in communication with a peptide analysis module (e.g., an electrospray tandem mass spectrometer or ESI- MS/MS) which is used to collect information relating to the properties of the individual peptides. One or more interfacing microfluidic modules also can be provided for interfacing the downstream separation module with the peptide analysis module.

In one aspect of the present invention, **the integrated microfluidic system for proteome analysis 31 further comprises a system processor** which can convert electrical signals obtained from different modules of the integrated microfluidic proteome analysis system 31 (and/or from their own associated processors or microprocessors) into information relating to separation efficacy and the properties of substantially separated proteins and peptides as they travel through different modules of the system. Preferably, the system processor also monitors the rates at which proteins/peptides move through different modules of the system. Preferably, signals are obtained from one or more detectors which are in optical communication with different modules and/or channels of the integrated microfluidic proteome analysis system 31. In one aspect of the present invention, the detectors are in communication with the upstream separation module and as such are able to deliver a sample plug to a correct location of the microfluidic module in order to undergo a digestion reaction.

The integrated microfluidic system for proteome analysis 31 can vary in the arrangements and numbers of components/modules within the system. For example, the number and arrangement of detectors can vary. In one aspect of the present invention, the protease digestion module can interface directly with the peptide analysis module without connection to an intervening downstream separation module and/or interfacing module or can interface to the downstream separation module and not an interfacing module, or to an interfacing module but not a downstream separation module. In some aspects of the present invention, the protease digestion module also can perform separation, eliminating the need for one or more separation functions of the upstream separation module. In still other aspects of the present invention, the interfacing module can be coupled to a separation module for connection to a peptide analysis module without connection to a microfluidic module. In this scenario, digested or partially digested polypeptides can be delivered to the separation module after being obtained from a protease

digestion device not connected to the integrated microfluidic system for proteome analysis 31, or less preferably, after being obtained from an on-gel digestion process.

In other aspects of the present invention, although the integrated microfluidic proteome analysis system 31 is described as being "integrated" in the sense that the different modules complement each others' functions, various components of the integrated microfluidic proteome analysis system 31 can be used separately and/or in conjunction with other systems. For example, components selected from the group consisting of: the upstream separation module, protease digestion module, downstream separation module, interfacing module, and peptide analysis module, and combinations thereof, can be used separately. Additionally, some modules can be repeated within the integrated microfluidic system for proteome analysis 31, e.g., there may be more than one upstream and/or downstream separation module, more than one protease digestion module, more than one interfacing module, more than one detector, and more than one peptide analysis module within the integrated microfluidic proteome analysis system 31. It should be obvious to those of skill in the art that many permutations are possible and that all of these permutations are encompassed within the scope of the invention. (Page 13, Line 6 - Page 15, Line 17).

As such, Applicant has amended each independent claim to require the first uncharged, coated column to engage a first microfluidic system for proteome analysis. The Xue et al. reference does NOT disclose engaging the Xue et al. device to such any system for proteome analysis; more specifically, the Xue et al. reference does NOT disclose utilizing the microfluidic system for proteome analysis disclosed in the Applicant's specification (and disclosed in Applicant's co-pending U.S. Application No. 10/273,494, the entirety of which is hereby incorporated herein by reference). As such, Applicant respectfully requests removal of Xue et al. as a 35 U.S.C. §102(e) reference.

Claims Rejected Under 35 U.S.C. §103(a):

The August 5, 2004 Office Action made several rejections under 35 U.S.C. §103(a). More specifically, the Office Action rejected: claims 3-5, 16-18, 26-28, and 35-37 under §103(a) as being unpatentable over Xue et al in view of U.S. Patent No. 5,089,106 to Karger et al.; claims 10, 23, 31 and 40 under §103(a) as being unpatentable over Xue et al in view of U.S. Published Application No. 2001/0045358 A1 to Kopf-Sill et al.; and claims 13, 14,42, and 43 under §103(a) as being unpatentable over Xue et al in view of U.S. Published Application No.

2002/0170825 A1 to Lee et al. As will be discussed below, the cited references, alone or in any combination, do NOT disclose, teach or suggest a device or method for separating a sample of anions and cations comprising an uncharged first column having a coating and an uncharged second column having a coating wherein the first uncharged column is engaged to a first microfluidic system for proteome analysis. As such, Applicant respectfully requests reconsideration of the above-identified rejection.

The Office Action cites the Lee et al. reference, stating:

> Lee et al disclose microfluidic systems **for two-dimensional protein separations in proteome analysis** (e.g. Figure 3, Paragraph 0033)
>
> It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the devices and methods of Xue et al by placing the channels (26 and 27) in communication with sample inlets to proteome analysis systems, such as those taught by Lee et al, because it would provide a more powerful analytical tool with an additional dimension of separation. (August 8, 2004 Office Action; Page 8)(Emphasis added).

With this Response, the Applicant has **amended each independent claim to require the first uncharged, coated column to be engaged to a first microfluidic system for proteome analysis.** Support for this amendment is discussed above. As such, Applicant respectfully disagrees with the Office Action's conclusion that a mere two-dimensional protein separation apparatus of the Lee et al. reference teaches the "microfluidic system for proteome analysis" described above. Further, the Applicant respectfully disagrees that there would be any motivation to combine the Lee et al. reference with the Xue et al. references. As such, Applicant respectfully requests reconsideration and allowance of all pending claims rejected under 35 U.S.C. §103.

"Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." M.P.E.P. 2143.01. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of

ordinary skill in the art." In re Kotzab, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). See also In re Fine, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992); M.P.E.P. 2143.01.

The Lee et al. reference discloses:

> The invention provides a microfluidic apparatus **for performing 2-D biomolecular separations**. The microfluidic 2-D device may include first and second planar substrates which include at least **a first dimension microchannel extending in a first direction and an array of second dimension microchannels extending in a second direction, preferably, orthogonal to the first dimension**. The ends of at least some of the microchannels are in fluid communication with a plurality of reservoirs. The substrates may further include a number of microchannels and reservoirs. The reservoirs are in electrical communication with a plurality of electrodes and voltage power sources. **The device enables two dimensional separations of proteins and other biomolecules. According to another aspect of the invention, an isoelectric point based separation is enabled in a first dimension, and a size based separation in a second dimension**. (the Lee et al. reference; Abstract)(Emphasis added).

As summarized in the passage above, the Lee et al. reference discloses a device capable of separating a sample by a first criteria and subsequently by a second criteria (i.e., first by an isoelectric point based separation and second by a size separation). **Such a device does not disclose, teach or suggest the microfluidic system for proteome analysis as disclosed in the Applicant's specification.** Moreover, there is no motivation in any of the cited references to combine the Lee et al. device with the Xue et al. The Xue et al. device never discloses or suggests the need to further separate the already separated anions or cations with a 2-D separation device such as the Lee et al. device; further, the Lee et al. reference never discloses or suggests the desire to combine the 2-D separation device of Lee et al. with any type of further separation device. As such, the Applicant submits that none of the cited references, alone or in any combination, disclose, teach or suggest a device capable of efficiently separating anions from cations wherein one of the uncharged, coated channels engages a microfluidic system for proteome analysis.

In summary, Applicant has amended each independent claim of the pending application to remove the various 35 U.S.C. §§102, 103 rejections. The amended claims now require a

device or method for separating anions from cations comprising a first uncharged, coated column and a second uncharged, coated column wherein the first uncharged, coated column is engaged to a first microfluidic system for proteome analysis. Applicant believes that these amendments clearly remove the §102 rejections in that none of the cited references expressly or inherently comprise each of the claimed limitations. Also, Applicants believe the §103 rejections have been overcome because none of the cited references, alone or in any combination, disclose each element of the claims as amended and further there is no motivation to combine the various references. As such, Applicant respectfully requests reconsideration and allowance of all pending claims.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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Amendments to the Drawings:

The attached 2 sheets of drawings include changes to FIGS. 1 and 2:

Sheet 1, which includes FIG. 1, replaces the sheet that includes FIG. 1.

Sheet 2, which includes FIG. 2, replaces the sheet that includes FIG. 2.

Attachment: 2 replacement sheet(s).

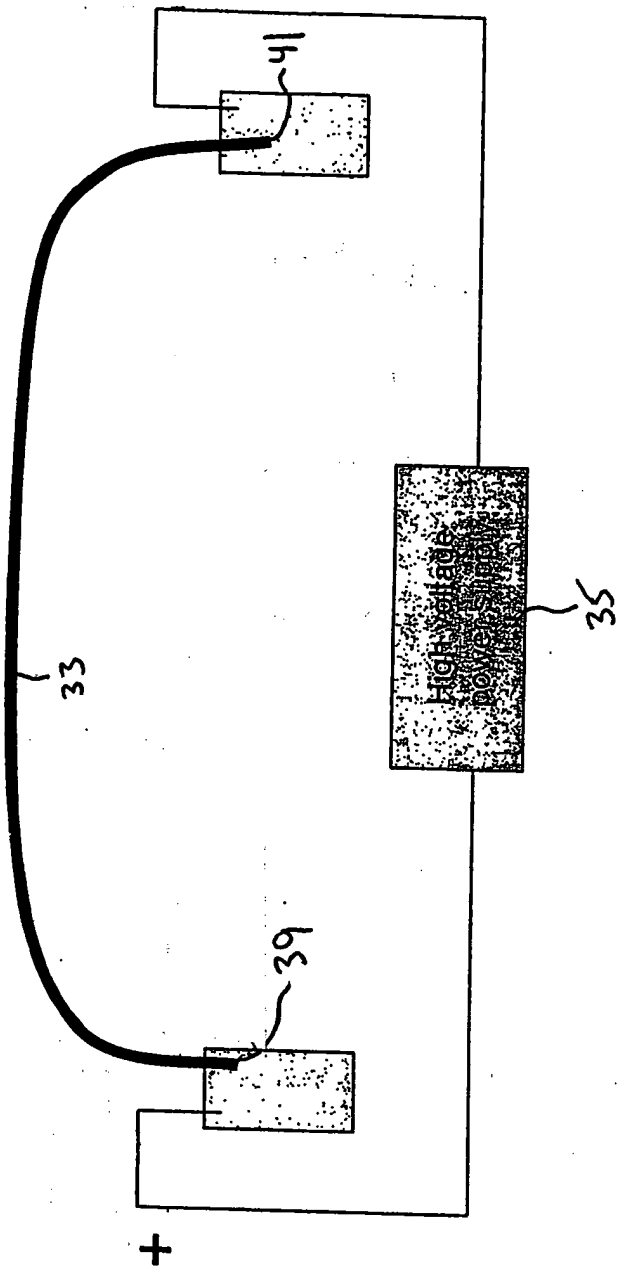

FIG. 1

Prior Art

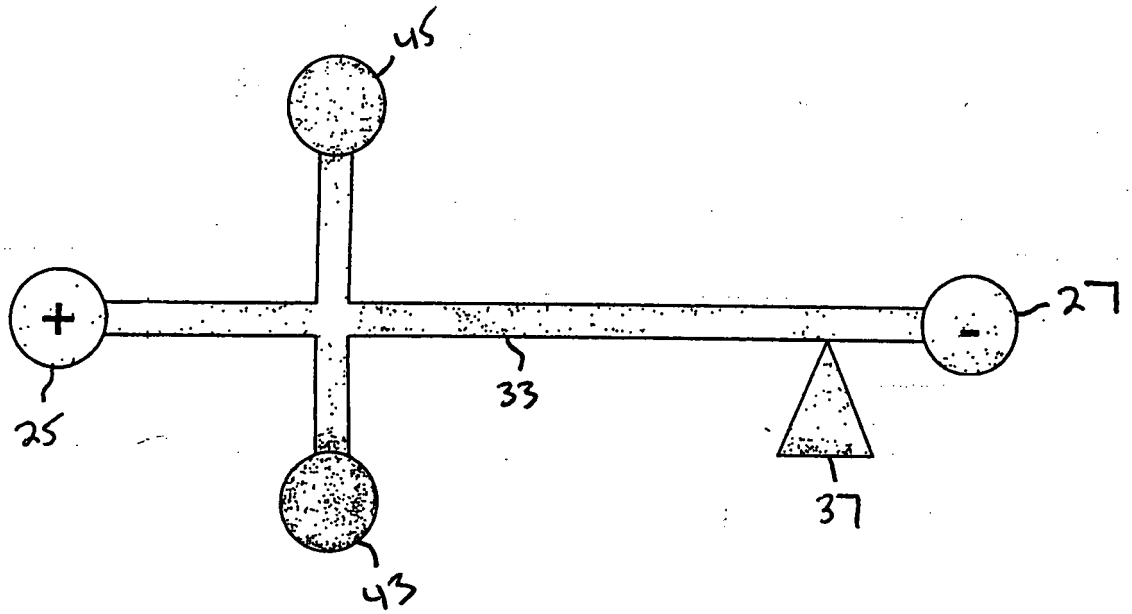

FIG. 2 Prior Art